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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,463	09/10/2004	David Selwood	GJE-6595	8237

23557 7590 10/30/2006

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/507,463	SELWOOD ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 7-12* is/are pending in the application.

4a) Of the above claim(s) *9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2 and 7-12* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. The amendment of 10 September 2004 to the disclosure and claims has been entered in full. Claims 3-6 are canceled. Claims 2 has been amended and new claims 7-12 have been added.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-2, 7-8, drawn to a peptide or its fragment that retains NP-1 (neuropilin-1) antagonist activity and a pharmaceutical composition comprising of the peptide.

Group II, claim(s) 9 and 10, drawn to a method for treating neurodegeneration by administration of the peptide.

Group III, claim(s) 11 and 12 drawn to a method for treatment of cancer by administration of the peptide.

This PCT rule defines special technical features as technical features that identify a contribution which each of the claimed inventions, considered as a whole, makes over prior art. Claims 1-2, 7-8 are anticipated by prior art. Li and Kagen (WO 01/85157; cited on the information disclosure statement of 17 August 2006) teaches a VEGF C-terminal fragment (24-51) that is 100% identical to the amino acid sequence of SEQ ID NO: 2 of the instant application (see Appendix A

- Li and Kagen). Therefore, claims 1, 2, 7 and 8 lack a special technical feature and cannot share one with the other claims.

3. The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I recites the special technical feature of the peptide or its fragment having NP-1 antagonist activity and a pharmaceutical composition comprising of the peptide, which is not required by the treatment methods of Groups II and III.

Group II recites the special technical feature of treating neurodegeneration comprising administration of the peptide to patients in such need, which is not required by the method of Group III.

Group III recites the special technical feature of providing anti-cancer therapy comprising administration of the peptide to patients in such need, which is not required by the method of Groups II.

4. In response to this Office Action/Election requirement, applicant must elect one from Groups I-III for consideration.

Notice of Rejoinder

5. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final

rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

6. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

7. Applicant is advised that in order for the reply to this requirement to complete it must include an election of the invention to be examined even though the requirement be traversed (37 C.F.R. 1.143).

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48 (b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. 1.48(b) and by the required under 37 C.F.R. 1.17(I).

9. During a telephone conversation with Mr. David Saliwanchik on 23 August 2006 a provisional election was made without traverse to prosecute the invention of Group I, claims 1, 2, 7 and 8. Affirmation of this election must be made by applicant in replying to this Office action. Claims 9-12 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

10. Claims 1, 2, 7 and 8 drawn to a to a peptide or its fragment that retains NP-1 antagonist activity and a pharmaceutical composition comprising of the peptide in cyclic or bicylic form, are under consideration in the instant application.

Sequence Compliance

11. The disclosure is objected to because of the following informalities: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Specifically, the amino acid sequences recited in claims 1, 7, and the abstract are not accompanied by the required reference to the relevant SEQ ID number (page 3, 13). Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Appropriate correction is required.

Specification

12. The abstract is objected to because of the following informalities:

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details (MPEP ¶ 6.16). The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied,

such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc. See MPEP § 608.01(b).

Appropriate correction is required.

The disclosure is objected to because of the following informalities: "Brief Description of Drawings" section is missing in the disclosure.

Appropriate correction is required.

Claim Objections

13. Claims 1 and 7 are objected to because of the following informalities: Acronym "NP-1" recited should be spelled out in all independent claims for clarity. Appropriate correction is required.

Claim Rejections

35 USC § 101 – Non-statutory subject matter

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

14. Claims 1 and 2 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a product of nature in that the claimed peptide is not "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193

(1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated", or "purified" or "synthesized" as taught by (page 4, lines 26-32) the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1, 2, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide having the amino acid sequence of SEQ ID NO: 2 in cyclic or bicyclic form that retains NP-1 (neuropilin-1) antagonist activity, does not reasonably provide enablement for fragments of SEQ ID NO: 2 having NP-1 antagonist activity. Furthermore the claims (7 and 8) do not provide enablement for a pharmaceutical composition comprising the peptide of SEQ ID NO: 2 or fragments thereof in cyclic or bicyclic form. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

16. The claims are directed to a cyclic or bicyclic peptide of the amino acid sequence of SEQ ID NO: 2 or a fragment thereof, having NP-1 antagonist

activity. The claims further recite a pharmaceutical composition comprising the above peptide or fragments thereof in cyclic or bicyclic form.

17. The specification of the instant application teaches a novel peptide in bicyclic form (EG3287) of SEQ ID NO: 2, having 28 amino acids, and fragments and variants thereof, that corresponds to amino acids 138-165 within VEGF (vascular endothelial growth factor) (page 2, lines 10-23; page 9, lines 30-31). The specification also teaches that NP-1, a non-tyrosine kinase transmembrane protein that specifically binds to $VEGF_{165}$, is expressed in certain tumor cells and plays a role in the growth and migration of axons during development (page 1, lines 19-27). Furthermore, the specification teaches that EG3287 exhibits specific NP-1 antagonist activity by competing with semaphorin 3, an axonal guidance polypeptide, and also suggests that it can be used as a treatment for various VEGF-induced diseases (page 2, lines 10-11; page 3, lines 16-17, 25-32; page 4, lines 3- 10). However, the specification does not teach any methods or working examples to indicate that all possible fragments of SEQ ID NO: 2 in cyclic or bicyclic form, will retain NP-1 antagonist activity. Undue experimentation would be required of the skilled artisan to determine such. The specification does not teach the specific peptide domains necessary for preserving the NP-1 antagonist activity. Thus, undue experimentation would be required of the skilled artisan to identify the precise structural and functional characteristics of EG3287 proteins retaining the NP-1 antagonist property.

18. Relevant literature states that NP-1 has neurotrophic activities and high

levels of mRNA and protein are expressed in the dorsal root ganglion (DRG) (Cheng et al., J Biol Chem. 279: 30654-30661, 2004). Cheng et al. further teach that EG3287, a peptide corresponding to the COOH-terminal residues of exon 7 and all of exon 8 of $VEGF_{165}$, inhibits the binding of radiolabeled $VEGF_{165}$ to NP-1 (page 30657, figure 3A and 3B), and blocks the inhibition of growth cone collapse by VEGF in the newborn rat DRG explants (page 30658, figure 4). The literature also teaches that EG3287 specifically inhibits NP-1 binding to $VEGF_{165}$ in porcine aortic endothelial cells and breast carcinoma cells (Jia et al., J Biol Chem. 281: 13493-15502, 2006). However, it is not even clear from the relevant prior and post-filing date literature as to what specific regions of the EG3287 peptide sequence or the maximum length of the sequences are essential for biological activity. Thus, undue experimentation would be required of the skilled artisan to identify the precise structural characteristics of EG3287 fragments that retain NP-1 antagonist properties.

19. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct

three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the EG3287 peptide which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

20. Furthermore the Examiner has interpreted the term "pharmaceutical" in claims 7 and 8 as an intended use. However, the specification does not provide

enablement for a pharmaceutical composition comprising the peptide of SEQ ID NO: 2 or fragments thereof in cyclic or bicyclic form. Relevant literature as stated above only teaches in vitro experiments to demonstrate the inhibition of VEGF binding to cells specifically expressing NP-1. The literature and instant specification do not teach in vivo studies to demonstrate therapeutic implications of the claimed peptide in specific disorders. In vitro experiments such as that described in the instant application, are vastly different from in vivo assays, both physiologically or biologically, and in predictability of success, and thus would entail undue experimentation by a skilled artisan (See *Maas*, 9 USPQ2d 1746). The *in vivo* therapeutic use of the 28 mer peptide of SEQ ID NO: 2 or its fragments in cyclic form, formulated into a pharmaceutical composition, and retaining NP-1 activity, would involve undue experimentation of one skilled in the art. (Please note that this issue could be overcome by removing the term "pharmaceutical" from the claims).

21. Due to the large quantity of experimentation necessary to generate the infinite number of fragments of SEQ ID NO: 2 recited in the claims and screening such for NP-1 inhibiting activity, and to administer the proteins for treatment; the lack of direction/guidance presented in the specification regarding the same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural or functional limitations - undue experimentation would be required of the skilled artisan to make and/or

use the claimed invention.

Claim Rejections - 35 USC § 112, first paragraph- Written Description

22. Claims 1, 2, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

23. The claims are directed to a cyclic or bicyclic peptide of the amino acid sequence of SEQ ID NO: 2 or a fragment thereof, having NP-1 antagonist activity. The claims further recite a pharmaceutical composition comprising the above peptide or fragments thereof in cyclic or bicyclic form.

24. The specification of the instant application teaches a novel peptide in bicyclic form (EG3287) of SEQ ID NO: 2, having 28 amino acids, and fragments and variants thereof, that corresponds to amino acids 138-165 within VEGF (vascular endothelial growth factor) (page 2, lines 10-23; page 9, lines 30-31). The specification also teaches that NP-1, a non-tyrosine kinase transmembrane protein that specifically binds to $VEGF_{165}$, is expressed in certain tumor cells and plays a role in the growth and migration of axons during development (page 1, lines 19-27). Furthermore, the specification teaches that EG3287 exhibits specific NP-1 antagonist activity by competing with semaphorin 3, an axonal guidance polypeptide, and also suggests that it can be used as a treatment for various

VEGF-induced diseases (page 2, lines 10-11; page 3, lines 16-17, 25-32; page 4, lines 3- 10). However, the claims do not require that the peptide posses any biological activity, nor any particular conserved structure. Thus, the claims are drawn to a genus of peptides, and methods using the genus of peptides.

25. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The specification has not shown a relationship between the structure, function, or properties of the claimed genus of polypeptides. However, in this case, the only factor present in the claim is a recitation of inhibition of NP-1 activity. There is not even identification of any particular portion of the EG3287 peptide structure of SEQ ID NO: 2that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The brief description in the specification of one EG3287 peptide (SEQ ID NO: 2) is not adequate written description of an entire genus of functionally equivalent polypeptides, which incorporate all fragments of EG3287 peptide.

26. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing

date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

27. With the exception of the EG3287 peptide sequence referred to above (SEQ ID NO: 2), the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or production. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The *polypeptide itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

28. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

29. Therefore, only the EG3287 peptide comprising the amino acid sequence of SEQ ID NO: 2, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112-Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

30. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

31. Claim 8 recites the limitation "pharmaceutical composition" in line 1. There is insufficient antecedent basis for this limitation in the claim as there is no pharmaceutical composition in claim 1. (Please note that this issue could be overcome by amending the claim to recite, for example "claim 7" rather that "claim 1").

Claim Rejections - 35 USC § 103

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

33. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any

inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

34. Claims 1, 2, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li and Kagen (International Publication No. WO200185157-A1, published on 15 November 2001), in view of Achen et al., (US Patent Application Publication No. US2002/0065218 A1, published on 30 May 2002).

35. The claims are directed to a cyclic or bicyclic peptide of the amino acid sequence of SEQ ID NO: 2 or a fragment thereof, having NP-1 antagonist activity. The claims further recite a pharmaceutical composition comprising the above peptide or fragments thereof in cyclic or bicyclic form.

36. Li and Kagen teach a $VEGF_{165}$ C-terminal linear protein fragment (amino acids 24-51), that is 100 percent identical to SEQ ID NO: 2 of the instant specification (see Appendix A).

37. Li and Kagen do not teach the peptide in cyclic or bicyclic form.

38. Achen et al. teaches monocyclic and bicyclic peptide inhibitors of VEGF-D and pharmaceutical compositions comprising the peptides (page 1, para 0002; page 4, para 0040-0045).

39. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the linear VEGF peptide of Li and Kagen followed by cyclisation of the peptides as taught by Achen et al. The person of ordinary skill in the art would have been motivated to generate cyclic peptide molecules because structural modifications of peptides result in "improved activity, stability and bioavailability" (Achen et al., page 5, para 0049). The person of ordinary skill in the art would have expected success because cyclisation procedures were already being performed in the art at the time the invention was made.

40. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

41. No claims are allowed.

42. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

43. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

44. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
October 6, 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER

APPENDIX A

RESULT 2
AAE15417
ID AAE15417 standard; protein; 51 AA.
XX
AC AAE15417;
XX
DT 12-MAR-2002 (first entry)
XX
DE Human vascular endothelial growth factor 165 C-terminal protein fragment.
XX
KW Human; prophylaxis; therapy; cellular proliferation; lysyl oxidase; LO;
KW microorganism infection; angiogenesis; replication; teratocarcinoma;
KW germ cell tumour; osteosarcoma; fibrosarcoma; angiogenic disease; AIDS;
KW acquired immune deficiency syndrome; hyperplastic disease; inflammation;
KW cancer; melanoma; lesion; wound; HIV-1; human immunodeficiency virus;
KW vascular endothelial growth factor; VEGF165.
XX
OS Unidentified.
XX
FH Key Location/Qualifiers
FT Domain 9. .51
FT /note= "Lysine and arginine-rich basic domain"
XX
PN WO200185157-A1.
XX
PD 15-NOV-2001.
XX
PF 10-MAY-2001; 2001WO-US015191.
XX
PR 10-MAY-2000; 2000US-0202568P.
XX
PA (UYBO-) UNIV BOSTON.
XX
PI Li W, Kagen HM;
XX
DR WPI; 2002-062187/08.
XX
PT Composition for prophylaxis and treatment of a condition associated with
PT abnormal cellular proliferation, angiogenesis or microorganism infection,
PT comprises active portion of an inhibitor, preferably lysyl oxidase.
XX
PS Disclosure; Fig 1; 97pp; English.
XX
CC The patent discloses compositions and methods for prophylaxis and
CC treatment of conditions associated with abnormal cellular proliferation,
CC angiogenesis or microorganism infection. The composition comprises an
CC active portion of an inhibitor, preferably lysyl oxidase (LO) which
CC inactivates and oxidises a growth factor, angiogenic factor or a trans-
CC activator for replication of the microorganism. The compositions of the
CC invention are useful for prophylaxis and treatment of conditions such as
CC cancers of the breast, colon, renal, prostate, ovary, lung, brain,
CC uterus, skin, embryo carcinoma, teratocarcinoma, germ cell tumour,
CC osteosarcoma, fibrosarcoma, melanoma, angiogenic diseases, AIDS (acquired
CC immune deficiency syndrome)-associated malignancies, other tumours and
CC hyperplastic diseases with or without inflammation. It is also useful for
CC treating diseases associated with angiogenesis, abnormal cellular
CC proliferation, preferably human cell proliferation (e.g., tumour, lesion
CC or wound), angiogenesis or conditions associated with microorganism
CC infection such as AIDS caused by HIV-1. It is useful for modulating
CC cellular proliferation and angiogenesis by contacting mitogenic and
CC angiogenic factor and determining regulation of cell proliferation. The

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CC   present sequence is vascular endothelial growth factor (VEGF) 165 C-
CC   terminal protein fragment. VEGF is a substrate for LO. The oxidation of
CC   lysine residues of VEGF by LO dramatically reduces their mitogenic
CC   potential and thus inhibits normal and tumour cell growth
XX
SQ   Sequence 51 AA;

  Query Match             100.0%;  Score 157;  DB 5;  Length 51;
  Best Local Similarity   100.0%;  Pred. No. 7.6e-13;
  Matches   28;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 SCKNTDSRCKARQLELNERTCRCDKPRR 28
              ||||||||||||||||||||||||||||
Db         24 SCKNTDSRCKARQLELNERTCRCDKPRR 51
```